

## Risk of Breast Cancer in Men With Liver Cirrhosis

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**Objective:** Liver cirrhosis is associated with increased levels of estrogens, which may be causally related to breast cancer. Because background estrogen levels are lower in men than in women, an estrogen-mediated link between liver cirrhosis and breast cancer would be easier to detect in men. **Methods:** Men hospitalized with liver cirrhosis in Denmark from January 1, 1977, to December 31, 1989, were followed up, through record linkage, until the end of December 1993 for the possible occurrence of breast cancer. **Results:** A total of 11,642 men with liver cirrhosis were identified and were followed for a mean period of 4.3 yr, for a total of 49,687 person-years. Three cases of male breast cancer were observed whereas 0.75 was expected, for a standardized incidence ratio of 4.0 (95% confidence interval, 0.8–11.7). **Conclusions:** Cirrhosis, possibly via high levels of endogenous estrogens, increases the risk of breast cancer in men. (Am J Gastroenterol 1998;93:231–233. © 1998 by Am. Coll. of Gastroenterology)

### INTRODUCTION

Breast cancer in men is a rare disease that has received relatively little attention in the epidemiological literature (1). Notable similarities in geographical patterns between male and female breast cancer incidence (2, 3) suggest that these cancers may share etiological and/or pathogenic components. Similar to current thinking about the etiology of female breast cancer, endogenous and exogenous estrogens are likely to play an important role in men, although the specific mechanisms have not been identified. Documentation of an association between elevated estrogen levels and subsequent onset of male breast cancer would be essential in clarifying the etiology in men, but may also help elucidate the etiology of breast cancer in women. Unfortunately, previous small case-control studies of male breast cancer have not identified specific hormones or related metabolites that differ consistently between cases and controls (4–6).

The rarity of breast cancer in men has precluded the performance of biochemical determinations in prospective cohort investigations. However, hyperestrogenemia is frequently present among men with liver cirrhosis (7–9), and case-control investigations have indicated that this disease could increase the risk of male breast cancer (10). Computerized nationwide registration systems in Denmark allowed us to undertake a population-based prospective evaluation of the association, if any, between liver cirrhosis and the subsequent occurrence of breast cancer in men.

### MATERIALS AND METHODS

The Danish National Registry of Patients was established in 1977 and covers 99.4% of all discharges from hospitals anywhere in the country (11). Recorded information includes the civil registration number (CRN) that is unique to every Danish citizen, dates of admission and discharge, and up to 20 discharge diagnoses, classified according to the Danish version of the International Classification of Diseases, 8th edition (ICD-8) (12). Discharge records were linked through the CRN. All male members in the National Registry of Patients from January 1, 1977, to December 31, 1989, were enrolled in the study if the discharge diagnosis in at least one of their hospitalizations was cirrhosis of the liver (ICD 571.09, alcoholic cirrhosis; 571.90, primary biliary cirrhosis; 571.92, unspecified cirrhosis; 571.99, nonalcoholic cirrhosis; 571.93, cirrhosis based on chronic hepatitis). Follow-up time was measured from the earliest among the relevant discharge dates. Cohort members were considered to have alcohol-related cirrhosis if this was one of the explicitly stated discharge diagnoses (ICD 571.09) or if alcoholism (ICD 303) was mentioned in any of the discharge records of the patient.

All members of the study cohort were linked through their CRN to the nationwide Cause of Death Registry and the Cancer Registry. Patients were followed until date of death or December 31, 1993. Observed, histologically confirmed incident cases of male breast cancer were compared with expected cases, calculated using age- and calendar-specific incidence rates of this disease in Denmark.

## RESULTS

A total of 11,642 male patients with liver cirrhosis were followed for a mean period of 4.3 yr, for a total of 49,687 person-years. For 7,755 patients, there was an indication that their liver cirrhosis was associated with excess alcohol intake. A total of three cases of male breast cancer were identified after a follow-up time of 4 months, 4 yr, and 7 yr, respectively. The expected number was 0.75. The standardized incidence ratio was 4.0, with 95% confidence interval 0.8–11.7, according to exact Poisson limits (13). Two of the men with breast cancer were diagnosed among the patients with alcoholic cirrhosis, and one among the patients with nonalcoholic cirrhosis.

## DISCUSSION

Male breast cancer is a rare disease; the incidence in Denmark is about five per 1,000,000 person-years (14). Small numbers have imposed statistical power limitations on epidemiological investigations, and there is uncertainty about the risk profile of the disease. Obesity, gynecomastia, and Klinefelter syndrome are likely to be genuine risk factors for breast cancer in men (1, 5), whereas the evidence is weak that heat or extremely low-frequency electromagnetic fields may increase the risk of this disease (15, 16).

The present study also has power limitations, but the central finding supports the working hypothesis, which was *a priori* unidirectional. Moreover, selection bias is unlikely in a design that relies on computerized linkage of databases with almost complete nationwide coverage. Information bias would be possible if men with liver cirrhosis were under increased surveillance for the possible development of breast cancer, but the association of the two conditions has not been generally recognized, and the likelihood of this bias should be small in an adequately functioning health care system with universal coverage. Confounding is certainly possible, but no candidate factor with the required properties is immediately obvious; such a factor would have to be fairly common as well as independently and strongly associated with both liver cirrhosis and male breast cancer. It appears likely that the documented association is genuine.

Cirrhosis of the liver is a pathologically heterogeneous entity, with several pathophysiological manifestations. However, hyperestrogenism is a salient characteristic of liver cirrhosis (7–9) and has been invoked to explain the association of this disease with other conditions, in particular gynecomastia and cholelithiasis (1, 17). Hyperestrogenemia is likely to be the mechanism that links liver cirrhosis to breast cancer in men. This interpretation is supported by the findings of a case-control study that evaluated serum estrogens (4), although no significant difference was found in two more recent case-control investigations (5, 6). Some support is also provided by the report that two men have developed breast cancer after prolonged administration of

estrogen treatment for cancer of the prostate (18), as well as from biochemical considerations (19).

Studies of liver cirrhosis in relation to breast cancer among women may not be as informative as those among men if estrogens are the critical mediators, because background levels and the associated variability of these hormones are substantially higher in women. Most studies in women have focused on primary biliary cirrhosis, which is more common among women than among men. Two studies have found a significant increase of breast cancer incidence in women with primary biliary cirrhosis (20, 21), but no association was evident in a large population-based study from Sweden (22).

In conclusion, our study indicates that liver cirrhosis increases the risk of breast cancer in men, supporting the hypothesis proposed on the basis of theoretical considerations, isolated case reports (23), and suggestive data from case-control investigations (4, 10). The hyperestrogenicity that characterizes liver cirrhosis in men appears to be the likely mediating mechanism.

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